

## General

### Guideline Title

Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline.

### Bibliographic Source(s)

Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, Lin NU, Modi S, Patt DA, Perez EA, Perlmutter J, Ramakrishna N, Winer EP. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99. [52 references] [PubMed](#)

### Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Recommendations

### Major Recommendations

Definitions for the rating of evidence (High, Intermediate, Low, Insufficient); types of recommendations (Evidence-Based, Formal Consensus, Informal Consensus, No Recommendation); and strength of recommendations (Strong, Moderate, Weak) are provided at the end of the "Major Recommendations" field.

#### Clinical Question 1

What is the optimal treatment for patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer?

For patients with HER2-positive advanced breast cancer:

#### Clinical Question 1.A

Is HER2-targeted therapy recommended for all patients in the first-line setting?

*Recommendation 1.A.I.* Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with estrogen receptor (ER)-positive or progesterone receptor (PgR)-positive and HER2-positive disease, for whom clinicians may use endocrine therapy alone (see Clinical Question 2). Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

#### *Clinical Question 1.A.II*

Is HER2-targeted therapy recommended for all patients in the second-line setting?

*Recommendation 1.A.II.* If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend second-line HER2-targeted therapy-based treatment. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

*Clinical Question 1.A.III*

Is HER2-targeted therapy recommended for all patients in the third-line setting and beyond?

*Recommendation 1.A.III.* If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, clinicians should recommend third-line or greater HER2-targeted therapy-based treatment. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.

*Clinical Question 1.B*

Which HER2-targeted therapy (trastuzumab, lapatinib, pertuzumab, or trastuzumab emtansine [T-DM1]) with or without chemotherapy should be offered?

*Clinical Question 1.B.I*

What is the specific recommended regimen in the first-line setting?

*Recommendation 1.B.I.* Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

*Clinical Question 1.B.II*

What is the specific recommended regimen in the second-line setting?

*Recommendation 1.B.II.* If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend T-DM1 as a second-line treatment. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

*Clinical Question 1.B.III*

What is the specific recommended regimen in the third-line setting and beyond?

*Recommendation 1.B.III.a.* If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted therapy, but she has not received T-DM1, clinicians should offer T-DM1. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

*Recommendation 1.B.III.b.* If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, but she has not received pertuzumab, clinicians may offer pertuzumab. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

*Recommendation 1.B.III.c.* If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, and she has already received pertuzumab and T-DM1, clinicians should recommend third-line or greater HER2-targeted therapy-based treatment. Options include lapatinib plus capecitabine, as well as other combinations of chemotherapy and trastuzumab, lapatinib and trastuzumab, or hormonal therapy (in patients with ER-positive and/or PgR-positive disease). There is insufficient evidence to recommend one regimen over another. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

*Clinical Question 1.B.IV*

What is the optimal timing, dose, schedule, and duration of treatment?

The a priori clinical question for this guideline included optimal timing, dose, and schedule, but there was no specific evidence to inform the issues on optimal timing or dose; therefore, the guideline will not provide recommendations on these. Some conclusions, however, were drawn regarding duration.

*Recommendation 1.B.IV.* If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4 to 6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When

chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.

#### Clinical Question 1.B.V

How should any previous HER2 adjuvant therapy influence treatment?

##### Clinical Question 1.B.V.a

For patients with a recurrence  $\leq 12$  months after adjuvant treatment?

*Recommendation 1.B.V.a.* If a patient finished trastuzumab-based adjuvant treatment  $\leq 12$  months before recurrence, clinicians should follow the second-line HER2-targeted therapy-based treatment recommendations (Recommendation 1.B.II). Type: evidence-based. Evidence quality: intermediate. Strength of recommendation: moderate.

##### Clinical Question 1.B.V.b

For patients with a recurrence  $> 12$  months after adjuvant treatment?

*Recommendation 1.B.V.b.* If a patient finished trastuzumab-based adjuvant treatment  $> 12$  months before recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations (Recommendation 1.B.I). Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

#### Clinical Question 2

For patients with HER2-positive advanced breast cancer that is also ER positive ( $\pm$ PgR positive), does ER/PgR status influence decisions about the following:

##### Clinical Question 2.A

What is the most appropriate first-line therapy for patients with HER2-positive, ER-positive (PgR positive or negative) advanced breast cancer?

If a patient's cancer is hormone receptor positive and HER2 positive, clinicians may recommend either:

*Recommendation 2.A.I.* HER2-targeted therapy plus chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

*Recommendation 2.A.II.* Endocrine therapy plus trastuzumab or lapatinib (in selected cases). Type: evidence based. Evidence quality: high. Strength of recommendation: moderate.

*Recommendation 2.A.III.* Endocrine therapy alone (in selected cases; see Recommendation 2.C). Type: evidence based. Evidence quality: intermediate. Strength of recommendation: weak.

##### Clinical Question 2.B

If a clinician plans to offer endocrine therapy at some point during a woman's treatment, what is the appropriate sequencing?

*Recommendation 2.B.* If the patient has started with a HER2-positive targeted therapy and chemotherapy combination, clinicians may add endocrine therapy to the HER2-targeted therapy when chemotherapy ends and/or when the cancer progresses. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.

##### Clinical Question 2.C

Can clinicians offer first-line endocrine therapy? If so, should it always be in combination with HER2-targeted therapy?

*Recommendation 2.C.* In special circumstances, such as low disease burden, presence of comorbidities (contradictions to HER2-targeted therapy, such as congestive heart failure), and/or presence of a long disease-free interval, clinicians may offer first-line endocrine therapy alone. Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: weak.

#### Definitions:

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
<b>High</b>	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
<b>Intermediate</b>	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
<b>Low</b>	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
<b>Insufficient</b>	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

#### Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
<b>Low risk</b>	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
<b>Intermediate</b>	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
<b>High risk</b>	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

#### Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
<b>Strong</b>	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
<b>Moderate</b>	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
<b>Weak</b>	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

#### Guide for Types of Recommendations

Type of Recommendation	Definition
<b>Evidence based</b>	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
<b>Formal</b>	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the

Type of Recommendation	Definition
	Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
Informal consensus	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
No recommendation	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

## Clinical Algorithm(s)

A treatment algorithm is available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

## Scope

### Disease/Condition(s)

Advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer

### Other Disease/Condition(s) Addressed

- Estrogen receptor (ER)-positive breast cancer
- Progesterone receptor (PgR)-positive breast cancer

## Guideline Category

Management

Treatment

## Clinical Specialty

Oncology

Radiation Oncology

Surgery

## Intended Users

Advanced Practice Nurses

Allied Health Personnel

Nurses

Patients

Physician Assistants

## Guideline Objective(s)

To provide evidence-based recommendations to practicing oncologists and others on systemic therapy for patients with human epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer

## Target Population

Individuals with advanced human epidermal growth factor receptor 2 (HER2)-positive breast cancer

## Interventions and Practices Considered

1. Human epidermal growth factor receptor 2 (HER2)-targeted therapy
  - First-line: trastuzumab, pertuzumab, taxane combination
  - Second-line: trastuzumab emtansine (T-DM1), pertuzumab if not previously received
  - Third-line: lapatinib plus capecitabine, as well as other combinations of chemotherapy, and trastuzumab, lapatinib and trastuzumab, or hormonal therapy
2. Chemotherapy in combination with HER2-targeted therapy (depending on toxicity and absence of progression)
3. Endocrine therapy (alone or in combination with HER2-targeted therapy)

## Major Outcomes Considered

- Overall survival
- Progression-free survival (PFS)
- Adverse events

## Methodology

### Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

### Description of Methods Used to Collect/Select the Evidence

An American Society of Clinical Oncology (ASCO) systematic review in MEDLINE was conducted. Most of the recommendations are evidence based and rely on publications found in literature searches from 2009 to October 2012 (trastuzumab) and from 1966 to 2012 (nontrastuzumab agents). Literature on trastuzumab, specifically articles published before 2009, was included in an earlier Cancer Care Ontario (CCO) systematic review (see the Methodology Supplement [see the "Availability of Companion Documents" field]).

Articles were selected for inclusion in the systematic review of evidence if they met the following criteria: fully published or recent meeting presentations of English-language reports of phase III randomized controlled trials (RCTs) or rigorously conducted systematic reviews or meta-analyses; studies involving a population of patients with epidermal growth factor receptor 2 (HER2)-positive advanced breast cancer; and trials comparing a targeted agent ( $\pm$  chemotherapy and  $\pm$  endocrine therapy) with another treatment regimen, placebo, or observation. Meeting abstracts were included only if the presentation or poster was available.

Articles were excluded from the systematic review if they were: meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; and published in a language other than English.

# Number of Source Documents

A total of nine first-line, three second-line, and four beyond–second-line phase III randomized clinical trials were deemed eligible for inclusion in the American Society of Clinical Oncology (ASCO) systematic review of the results (some trials provided evidence for >one recommendation) and comprise the evidentiary basis of the guideline recommendations, in addition to the trials in the Cancer Care Ontario (CCO) systematic review.

# Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

## Rating Scheme for the Strength of the Evidence

Guide for Rating Strength of Evidence

Rating for Strength of Evidence	Definition
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits v harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.
Intermediate	Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.

Guide for Rating of Potential for Bias

Rating of Potential for Bias	Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials
Low risk	No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features are described clearly (including the population, setting, interventions, comparison groups, measurement of outcomes, and reasons for dropouts).
Intermediate	The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.
High risk	There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.

# Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

## Description of the Methods Used to Analyze the Evidence

Data Extraction

Literature search results were reviewed and deemed appropriate for full text review by an American Society of Clinical Oncology (ASCO) staff

member, in consultation with the Expert Panel Co-Chairs. Data were extracted by one reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary.

Study Quality

As seen in the quality assessment table (see Table 1 in the original guideline document), study quality was formally assessed for the 11 studies identified. Design aspects related to individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on generally indicating an intermediate to high potential risk of bias for most of the identified evidence. The Methodology Supplement provides definitions of ratings for overall potential risk of bias.

Methods Used to Formulate the Recommendations

Expert Consensus

Informal Consensus

Description of Methods Used to Formulate the Recommendations

The recommendations were developed by a multidisciplinary group of experts (see Appendix Table A1 in the original guideline document) using a systematic review of phase III randomized controlled trials (RCTs) and clinical experience as a guide.

The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software (<http://gem.med.yale.edu/BRIDGE-Wiz>). Ratings for type of recommendation and strength of evidence are provided in the Methodology and Data Supplements (see the "Availability of Companions Documents" field).

Detailed information about the methods used to develop this guideline, regarding the Expert Panel composition, guideline development process, and steps taken in the systematic review and recommendation development process, is available in the Methodology and Data Supplements).

There was insufficient evidence to make evidence-based recommendations on some of the clinical questions. Therefore, some recommendations were made on the basis of informal consensus and are labeled as such.

Rating Scheme for the Strength of the Recommendations

Guide for Strength of Recommendations

Rating for Strength of Recommendation	Definition
Strong	There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on (1) good evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with minor and/or few exceptions; (3) minor and/or few concerns about study quality; and/or (4) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on (1) limited evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, but with important exceptions; (3) concerns about study quality; and/or (4) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Guide for Types of Recommendations



Type of Recommendation	Definition
<b>Evidence based</b>	There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.
<b>Formal consensus</b>	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak"). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement (see the "Availability of Companion Documents" field).
<b>Informal consensus</b>	The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., "strong," "moderate," or "weak").
<b>No recommendation</b>	There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.

## Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

## Method of Guideline Validation

External Peer Review

Internal Peer Review

## Description of Method of Guideline Validation

All members of the Expert Panel participated in the preparation of the draft guideline document, which was then disseminated for external review and submitted to the *Journal of Clinical Oncology (JCO)* for peer review and publication. All American Society of Clinical Oncology (ASCO) guidelines are reviewed and approved by the ASCO Clinical Practice Guidelines Committee (CPGC) prior to publication.

The Clinical Practice Guideline Committee approved this guideline update on November 19, 2013.

## Evidence Supporting the Recommendations

### Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

## Benefits/Harms of Implementing the Guideline Recommendations

### Potential Benefits

Optimal management of patients with advanced human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer

### Potential Harms

- Toxic adverse effects of human epidermal growth factor receptor 2 (HER2)-targeted therapy
- See Table 3 and Table 4 in the original guideline document for further data concerning adverse effects.

## Contraindications

### Contraindications

- There are some contraindications to human epidermal growth factor receptor 2 (HER2)-targeted therapy, as a result of its cardiovascular toxicity effects (see Table 4 in the original guideline document). The single most important contraindication is a decreased left ventricular ejection fraction (LVEF) and/or clinical evidence of congestive heart failure arising from low LVEF. Among patients with congestive heart failure or low ejection fraction, the decision to use HER2-targeted therapy must be made on an individual basis, assessing the relative risks of cardiac dysfunction from a specific regimen versus disease progression. Therefore, the Expert Panel recommended that clinicians treat patients with clinical congestive heart failure or compromised LVEF on a case-by-case basis, assessing the relative risks of cardiac dysfunction versus disease progression.
- Because the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) regimen used a taxane, contraindications to the regimen included any contraindications to the use of a taxane, such as neuropathy, prior taxane hypersensitivity, and so on (see drug labels for other contraindications). The Data Supplement (see the "Availability of Companion Documents" field) provides further information.

## Qualifying Statements

### Qualifying Statements

- The clinical practice guideline and other guidance published herein are provided by the American Society of Clinical Oncology (ASCO) to assist providers in clinical decision making. The information herein should not be relied on as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Each recommendation reflects high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like *must*, *must not*, *should*, and *should not* indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO provides this information on an as-is basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.
- Because many patients for whom guideline recommendations apply present with multiple chronic conditions (MCCs), any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating treatment and follow-up plans (common chronic conditions for patients with breast cancer are listed in Data Supplement 5 [see the "Availability of Companion Documents"]). Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

## Implementation of the Guideline

### Description of Implementation Strategy

## Guideline Implementation

American Society of Clinical Oncology (ASCO) guidelines are developed to be implemented in a variety of health settings. Barriers to implementation and application of the guideline recommendations include factors such as the need to increase awareness among front-line practitioners and cancer survivors and also the need to provide adequate services in the face of limited resources.

This guideline does not consider cost-effectiveness analyses. The agents in this guideline are FDA approved and available; however, cost is an issue that may be appropriate to discuss with patients, because copayments and other expenses are insurance dependent and/or financial assistance may be available. Unfortunately, there are parts of the country where access to a medical oncologist might be limited, and because of reimbursement issues, some smaller practices are referring elsewhere for expensive treatments. There is also the issue of the uninsured who do not qualify for Medicaid or other financial assistance. ASCO provides resources on cost of care for your patient. Most practicing oncologists in the United States have used trastuzumab and lapatinib and are starting to gain experience with pertuzumab and trastuzumab emtansine (T-DM1). As with all new treatments, diffusion in the community must occur in time.

The guideline *Bottom Line* was designed to facilitate implementation of recommendations. This guideline will also be distributed through the ASCO Practice Guideline Implementation Network and other ASCO communications. ASCO guidelines are posted on the ASCO Web site and most often published in the *Journal of Clinical Oncology (JCO)*.

For more information on the ASCO implementation strategy, please see the [ASCO Web site](#) .

## Implementation Tools

Clinical Algorithm

Patient Resources

Quick Reference Guides/Physician Guides

Slide Presentation

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

## Institute of Medicine (IOM) National Healthcare Quality Report Categories

### IOM Care Need

Getting Better

Living with Illness

### IOM Domain

Effectiveness

Patient-centeredness

## Identifying Information and Availability

### Bibliographic Source(s)

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Giordano SH, Temin S, Kirshner JJ, Chandarlapaty S, Crews JR, Davidson NE, Esteva FJ, Gonzalez-Angulo AM, Krop I, Levinson J, Lin NU, Modi S, Patt DA, Perez EA, Perlmutter J, Ramakrishna N, Winer EP. Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol. 2014 Jul 1;32(19):2078-99. [52 references] [PubMed](#)

## Adaptation

Not applicable: The guideline was not adapted from another source.

## Date Released

2014 July 1

## Guideline Developer(s)

American Society of Clinical Oncology - Medical Specialty Society

## Source(s) of Funding

American Society of Clinical Oncology

## Guideline Committee

Systemic Therapy for Patients With Advanced HER2-Positive Breast Cancer Expert Panel

## Composition of Group That Authored the Guideline

*Expert Panel Members:* Sharon H. Giordano, MD (*Panel co-chair*), University of Texas MD Anderson Cancer Center, Houston, TX; Eric P. Winer, MD (*Panel co-chair*), Dana-Farber Cancer Institute, Boston, MA; Sarat Chandarlapaty, MD, PhD, Memorial Sloan Kettering Cancer Center, New York, NY; Jennie R. Crews, MD, PeaceHealth St Joseph Cancer Center, Bellingham, WA; Nancy E. Davidson, MD, University of Pittsburgh Cancer Institute and UPMC Cancer Center, Pittsburgh, PA; Francisco J. Esteva, MD, New York University Cancer Institute, New York, NY; Ana M. Gonzalez-Angulo, MD, MSc, University of Texas MD Anderson Cancer Center, Houston, TX; Jeffrey J. Kirshner, MD, Hematology/Oncology Associates of Central New York, East Syracuse, NY; Ian Krop, MD, PhD, Dana-Farber Cancer Institute, Boston, MA; Jennifer Levinson, Ponte Vedra Beach, FL; Nancy U. Lin, MD, Dana-Farber Cancer Institute, Boston, MA; Shanu Modi, MD, Memorial Sloan Kettering Cancer Center, New York, NY; Debra A. Patt, MD, MPH, Texas Oncology, Austin, TX; Edith A. Perez, MD, Mayo Clinic, Jacksonville, FL; Jane Perlmutter, PhD, Ann Arbor, MI; Naren Ramakrishna, MD, PhD, University of Florida Health Cancer Center at Orlando Health, Orlando, FL

## Financial Disclosures/Conflicts of Interest

### Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with the American Society of Clinical Oncology (ASCO) Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/rwc> ). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

### Author's Disclosures of Potential Conflicts of Interest

*Although all authors completed the disclosure declaration, the following author(s) and/or an author's immediate family member(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.* Employment or Leadership Position: None Consultant or Advisory Role: Sarat Chandarlapaty, Daiichi Sankyo (C); Francisco J. Esteva, Genentech (C), Novartis (C); Ian Krop, Genentech (U), Roche (U); Nancy U. Lin, Genentech (U), Novartis (C); Eric P. Winer, Novartis (U), Pfizer (U), Genentech (U), AstraZeneca (U) Stock Ownership: None Honoraria: Sarat Chandarlapaty, GlaxoSmithKline; Naren Ramakrishna, Brainlab AG Research Funding: Sarat Chandarlapaty, Puma; Ian Krop, Genentech, Roche; Nancy U. Lin, Genentech, GlaxoSmithKline, Array Biopharma, Novartis, Synta; Shanu Modi, Genentech, Novartis, Synta Pharmaceuticals; Edith A. Perez, Genentech, GlaxoSmithKline; Eric P. Winer, Genentech Expert Testimony: None Patents, Royalties, and Licenses: None Other Remuneration: Eric P. Winer, Genentech

## Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

## Guideline Availability

Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .

Print copies: Available from American Society of Clinical Oncology, Cancer Policy and Clinical Affairs, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; E-mail: [guidelines@asco.org](mailto:guidelines@asco.org)

## Availability of Companion Documents

The following are available:

- Systemic therapy for patients with advanced HER2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. Data supplement. Alexandria (VA): American Society of Clinical Oncology; 2014. 50 p. Electronic copies: Available from the [American Society of Clinical Oncology \(ASCO\) Web site](#) .
- Systemic therapy for patients with advanced HER2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. Methodology supplement. Alexandria (VA): American Society of Clinical Oncology; 2014. 7 p. Electronic copies: Available from the [ASCO Web site](#) .
- Systemic therapy for patients with advanced HER2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. Slide set. Alexandria (VA): American Society of Clinical Oncology; 2014. 27 p. Electronic copies: Available in [PDF](#)  and [PowerPoint](#)  from the ASCO Web site.
- Systemic therapy for patients with advanced HER2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. Summary of recommendations: Table 1. Alexandria (VA): American Society of Clinical Oncology; 2014. 10 p. Electronic copies: Available from the [ASCO Web site](#) .

## Patient Resources

The following is available:

- Treatment of metastatic HER2-positive breast cancer. American Society of Clinical Oncology (ASCO) care and treatment recommendations for patients. 2014 May 5. Electronic copies: Available from the [Cancer.Net Web site](#) .

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

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